3. RCE Submission

This RCE is in response to the final Office action having a mailing date of June 11, 2004.

Claims 18-63 are pending in the application with claims 18, 20, 22, 30, 32, 34, 35, 36, 37, 41, 43, 45, 46, 50, 52, 54, 55, 59, 61, and 63 being in independent form. Claims 35 and 46 have been amended. Claims 18, 19, 36, and 55-63 have been canceled. Claims 31, 42, and 51 have been amended to remove the "and/or" language. Claims 30, 32, and 34 have been amended to depend from claim 20. Claims 33, 44, and 53 have been amended to add a comma after "trimer." The amendments do not add new matter. Applicants respectfully request reconsideration and allowance of the claims.

35 U.S.C. §112, second paragraph

Claims 35-36 and 46-54 stand rejected under 35 U.S.C. §112, second paragraph as being indefinite for lack of specific hybridization conditions in the claims. Applicants have amended claims 35 and 46 to incorporate the hybridization conditions described in the specification at page 10, lines 1-3. Claim 36 has been cancelled. Applicants have fully addressed the Examiner's concerns and respectfully request that the rejection be properly removed.

35 U.S.C. §112, first paragraph

Claims 18-63 stand rejected under 35 U.S.C. §112, first paragraph as supposedly not enabling 80% or 90% variants. Applicants have cancelled claim 18 and 19 drawn to 80% variants. Claims 55-63 have been cancelled. Applicants believe the specification provides enabling support for claims to 90% variants.

The test of enablement is whether one skilled in the art could make or use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988); *In re Stephens,* 529 F.2d 1343, 188 USPQ 659 (CCPA 1976). The amount of experimentation that is permissible to provide enablement depends upon a number of factors, which include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the

predictability of the art, and (8) the breadth of the claims. *In re Wands,* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

The specification provides ample support to enable one of skill in the art to make and use the claimed invention, namely variants having at least 90% identity to SEQ ID NO:2 that retain the capacity to bind LDCAM and/or B7L-1. Applicants disclose the cDNA and protein sequences for the full-length LDCAM ORFs for two species of the genus – *i.e.*, the mouse and human orthologues of LDCAM, which share about 98% identity over the full-length of the proteins. The specification further characterizes the proteins by identifying important functional domains, such as the signal sequence, the extracellular and intracellular domains, and the transmembrane domains (see page 3, line 35 to page 5, line 17), as well as having binding sites for band 4.1 and PDZ family members (page 3, lines 22-25). The specification further characterizes the protein by distinguishing LDCAM from other proteins that have limited homology, such as B7L-1 (page 4, lines 16-18), poliovirus receptor, delta opoid binding protein, and adhesion molecules (page 4, lines 29-30). Example 4 describes expressing full-length human LDCAM in CV1/EBNA cells. Examples 5 and 6 describe using LDCAM/Fc construct for screening cell lines for LDCAM binding. Example 9 teaches how to make and use a LDCAM/Fc construct and provides a detailed description of the oligonucleotide primers used in the PCR reactions to create the fusion protein (see page 26, lines 9-16), as well as the mammalian cells used for expression (page 26, lines 17-18), and how to purify the fusion protein (lines 18-28).

The specification teaches that a LDCAM variant may have one or more deletions, insertions or substitutions (page 5, lines 23-26) or that a variant may comprise conservatively substituted sequences and gives specific examples of conservative substitutions (page 6, lines 1-8). The specification discloses the computer program for determining percent identity (page 5, lines 28-37). The specification goes on to teach at page 8, lines 5-18 that alterations of the native amino acid sequence may be accomplished by introducing mutations at particular loci by synthesizing oligonucleotides containing a mutant sequence flanked by restriction sites that enable ligation into the native sequence, and by site-specific mutagenesis procedures. Such methods were well known in the art at the time of Applicants' earliest effective filing date (*i.e.*, 8/7/1998). Moreover, the specification provides numerous citations on how to perform such

methods. The variant sequences are screened for biologically active variants using the assays taught in the specification. This type of experimentation was routinely performed in 1998.

The specification describes the biological activities of LDCAM and biological assays for assessing LDCAM function, including forming homodimers (Example 5, page 24), binding B7L-1 (Example 5, page 24), binding activated T-cells (Example 12, page 28), inhibition of ConA-induced T-cell proliferation (Example 13, page 31), inhibition of IL-2 and IFN-gamma from ConA and PHA-induced T-cells (Example 14, page 32), reducing expression of CD69, CD54, and CD25 on T- and B-cells (Example 15, page 32), and NK-cell expansion (Example 16, page 34). These assays may be used to screen for biologically active LDCAM variants. In August of 1998, screening of proteins for binding to other proteins (*i.e.*, binding of LDCAM variants to wild-type LDCAM or B7-1) in an ELISA or a cell-based format would be considered quite routine by one of skill in the art.

Applicants' disclosure satisfies the enablement requirement as determined by a balancing of the *Wands* factors. As to the quantity of experimentation, the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 190 USPQ 214 (CCPA 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). It is a fact that one of skill in the art in 1998 routinely performed mutagenesis on molecules and screened the resultant proteins for biological activity. As evidence of this, please see the enclosed article: Approaches to DNA Mutagenesis: An Overview; Ling, et al., *Analytical Biochemistry* 254, 157-178 (1997). As the Examiner is aware, a patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991).

The Examiner states at page 3 of paper no. 15 that "Statements in the specification to go forth and make mutant sequence without guidance as to where the changes should be introduced does not provide the skilled artisan with sufficient guidance" is without merit. As described above, the specification provides working examples on making LDCAM constructs, expressing the protein, purifying the protein, and testing them for biological activity. The specification also describes methods for making variant sequences. . With regards to variant sequences, Applicants' specification states at page 6, lines 2-7:

> Variants may comprise conservatively substituted sequences, meaning that a given amino acid residue is replaced by a residue having similar physiochemical characteristics. Examples of conservative substitutions include substitution of one aliphatic residue for another, such as Ile, Val, Leu, or Ala for one another, or substitutions of one polar residue for another, such as between Lys and Arg; Glu and Asp; or Gln and Asn. Other such conservative substitutions, for example, substitutions of entire regions having similar hydrophobicity characteristics, are well known.

It was well within the capacity of the skilled artisan in 1998 to identify amino acid residues in SEQ ID NO:2 that could be replaced with a conservative substitution and use site-directed mutagenesis, or other mutagenesis methods, to do this. Making random mutations was an accepted technique, as acknowledged in *Ling, et al.* As the Examiner knows, "[t]he test of whether experimentation is undue is not merely quantitative, since **a considerable amount of experimentation is allowed *if it is routine*** (*In re Angestadt and Griffin*, 190 USPQ 214; CCPA 1976). It is important to bear in mind that the random substitutions or deletions are not necessarily predictive of a biologically active variant. The random variants are screened for the capacity to form homodimers and/or bind B7L-1, as taught in Example 5. The variants having at least 90% identity that possess biological activity fall within the scope of the claims, those that do not, are excluded. The making of mutant sequences and screening for biological activity was routine in 1998 and therefore Applicants' disclosure satisfies the enablement requirement.

When the Examiner discusses the predictability of the art, the Examiner has inappropriately imposed a burden upon Applicant to disclose *the specific sequences* for biologically active variants. This is not the standard required by the Federal Circuit (and by extension, the USPTO): "It is impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species; **it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it.** *In re Grimme, Keil and Schmitz,* 124 USPQ 449, 502 (CCPA 1960 - emphasis added). **It is not necessary that a patent applicant test all the embodiments of an invention.** *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200, 18 USPQ 2d 1016 (Fed. Cir. 1991) *cert. denied* 502 U.S. 856 (1991); *In re Angstadt*, 190 USPQ 214, 218 (CCPA – emphasis added). Moreover, because an application speaks to those skilled in the art, it **need not set forth every minute detail regarding the invention.** DeGeorge v. Bernier , 768

F.2d 1318, 1323 [226 758, 762] (Fed. Cir. 1985 – emphasis added). **As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of Section 112 is satisfied.** *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970 – emphasis added).

And finally, the Federal Circuit has spoken on the very subject at hand. In *Ex parte Mark*, the Examiner's position was that the claims encompassed innumerable muteins, while only a limited number of successful embodiments had been shown. The Examiner further asserted that undue experimentation would be required to generate the muteins encompassed by the claim using site-specific mutagenesis, and to test the resulting muteins for biological activity. **In reversing the Examiner, the Board noted that 'When it is considered that the claims.....all require that the mutein produced retain the biological activity of the native protein, we consider the disclosure of this application to be enabling.....'** *Ex parte Mark*, 12 USPQ2d 1904, 1906-1907 (BPAI 1989).

Applicants have shown that the specification satisfies the legal requirement for an enabling disclosure. As such, Applicants request that the rejection under 35 U.S.C. §112, first paragraph be withdrawn.

35 U.S.C. §102

Claims 18-63 stand rejected under 35 U.S.C. §102(e1) and (e2) as being anticipated by U.S. Patent Appln. Pub. No. 2002/0198147 and USPN 6,642,360, respectively. The Examiner states that the prior art teaches antibodies that bind to the PRO355 polypeptide (SEQ ID NO:61), which shares 99.1% identity with Applicants' SEQ ID NO:2. The Examiner notes that Applicants' SEQ ID NO:4 shares 97.8% identity with the PRO355 protein sequence. Based on the percent identity between Applicants' protein sequences and the PRO355 sequence, the Examiner believes that the antibodies taught in the prior art (and claimed in U.S. Patent Appln. Pub. No. 2002/0198147) are the same antibodies that Applicants are now claiming. Applicants respectfully disagree.

Applicants submit that USPN 6,642,360 and U.S. Patent Appln. Pub. No. 2002/0198147 are not prior art because Applicants' date of invention antedates the earliest

effective filing date of the references. As evidence, Applicants submit the enclosed Declaration under 37 CFR §1.131, which shows that Applicants were in possession of SEQ ID NO:2 and 4 prior to December 3, 1997, which is prior to the earliest effective filing date for either of the cited references. Consequently, USPN 6,642,360 is not prior art and the rejection under 35 U.S.C. §102(e2) may be properly withdrawn.

As to the rejection under 35 U.S.C. §102(e1) that U.S. Patent Appln. Pub. No. 2002/0198147 anticipates the present claims, Applicants note that U.S. Patent Appln. Pub. No. 2002/0198147 has been abandoned and therefore obviates the need for declaring an Interference Proceeding.

Applicants kindly request reconsideration and allowance of the claims. If any outstanding issues remain that may be easily reconciled, the Examiner is invited to telephone Applicants' representative at the number provided below.

Respectfully submitted,

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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this correspondence is being facsimile transmitted to the United States Patent and Trademark Office on the date indicated below.

Signed: Nanci M. Kertson Date: May 18, 2005
Nanci M. Kertson

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